Amdoxovir

Drug Class: **Nucleoside Reverse Transcriptase Inhibitors**

Drug Description

Amdoxovir, also known as AMDX or DAPD, is a dioxolane guanosine nucleoside analogue prodrug. Amdoxovir and its phosphorylated metabolite are potent nucleoside reverse transcriptase inhibitors (NRTIs) with activity against HIV-1, including against multi-drug-resistant virus. [1] [2] [3]

HIV/AIDS-Related Uses

Amdoxovir is an investigational NRTI. Amdoxovir was being tested in three studies (one Phase I for pharmacokinetics, one Phase I/II, and one Phase II) for the treatment of HIV-1 infection in adults who are treatment naive and in those who have experienced virologic failure on previous antiretroviral (ARV) regimens. In clinical studies, amdoxovir has been administered as monotherapy [4] , in combination with other ARV agents [5] [6] [7] , or with concomitant mycophenolate mofetil (MMF).[8] [9] Amdoxovir also displays activity against HIV-2.[10]

Amdoxovir was being developed under a licensing agreement between Emory University, the University of Georgia Research Foundation, and Gilead Sciences. On January 28, 2004, Gilead announced that it was ending its agreement with Emory and the University of Georgia but that it would meet its ongoing obligations with respect to existing clinical trials.[11] RFS Pharma, incorporated in 2004, now owns the license to amdoxovir and is actively studying the drug in HIV infected patients.[12]

Non-HIV/AIDS-Related Uses

Amdoxovir has activity against hepatitis B virus (HBV) in cell cultures and in humans.[13] It is in Phase II trials for the treatment of HBV.(2) When tested in laboratory animals, amdoxovir displayed stronger inhibitory effects against HBV when given in combination with other antiviral agents than when given as monotherapy.[14]

Pharmacology

Amdoxovir is a purine nucleoside analogue that is deaminated in vivo by adenosine deaminase to form the metabolite (-)-beta-D-dioxolane guanine (DXG). DXG, after conversion to its triphosphate form, is a potent and selective inhibitor of HIV-1 reverse transcriptase and also acts as a viral DNA chain terminator.[15] [16] [17] In vitro tests of DXG-triphosphate demonstrated anti-HIV-1 activity that was comparable with that of lamivudine or abacavir, less than that of zidovudine and emtricitabine, and greater than that of stavudine, didanosine, or adefovir.[18]

Amdoxovir is rapidly absorbed and converted to DXG following oral dosing. Amdoxovir and DXG concentrations increase in a dose-dependent manner. Peak plasma concentrations of both occur within 1 to 2 hours after dosing.[19] [20] Amdoxovir has a half-life of approximately 1 to 2 hours and is eliminated from plasma primarily by conversion to DXG. DXG has a plasma half-life of approximately 4 to 7 hours.[21]

Toxicology studies in animals have shown that amdoxovir and DXG are excreted by the kidneys. The limited aqueous solubility of amdoxovir and DXG results in precipitation as urine is concentrated. Patients with renal insufficiency may be at greater risk for obstructive nephropathy and should not receive amdoxovir until additional clinical testing is completed.[22] [23]

Amdoxovir differs structurally from currently approved NRTIs by the replacement of the 3' carbon of the carbohydrate moiety with an oxygen atom. In vitro analysis indicated that HIV-1 strains resistant to zidovudine, lamivudine, didanosine, zalcitabine, and abacavir was susceptible to DXG. Virus resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) was also susceptible to DXG, as was virus containing the multidrug-resistance-associated mutation G333E and the SS insertion between codons 68 and 69. Virus containing a K65R and Q151M double mutation was fully resistant to DXG, whereas virus containing either mutation alone was moderately resistant.[24] [25] The L74V mutation also conferred DXG resistance.[26]

Amdoxovir

Pharmacology (cont.)

The K65R and L74V mutations conferred cross resistance between DXG and other NRTIs in vitro. These data suggest that DXG should not be used in combination with 2',3'-dideoxynucleosides that select for the same resistance mutations. K65R and L74V mutations did not affect sensitivity to zidovudine. In fact, these mutations decreased zidovudine resistance when introduced into a zidovudine-resistant genetic background. The lack of cross resistance to zidovudine and the decrease in zidovudine resistance by DXG-resistant mutations provide strong rationale for the use of zidovudine and amdoxovir in combination.[27] In humans, amdoxovir resistance is also associated with K65R and L74V mutations. However, amdoxovir 500 mg twice daily was effective in patients with NRTI-resistant viral strains, including those with thymidine analogue mutations and with the M184V mutation.[28]

A Phase I study of amdoxovir monotherapy in treatment-experienced and treatment-naive patients indicated that viral load reduction is more modest in treatment-experienced patients than in treatment-naive patients.[29] Another early study evaluated amdoxovir 300 or 500 mg added to existing ARV therapy in 18 treatment-experienced patients with highly resistant HIV (median five NRTI mutations). The overall median viral load decrease at 12 weeks was 0.9 log.[30]

A 22-day study of amdoxovir in 90 treatment-naive and treatment-experienced patients evaluated 15 days of treatment with amdoxovir 100, 200, 300, or 500 mg twice daily or 600 mg once daily as monotherapy, compared with amdoxovir 300 or 500 mg twice daily in addition to existing ARV treatment. Median viral load reduction was 1.5 log with the highest doses in treatment-naive patients. Treatment-experienced patients had a 0.7 log viral load reduction with amdoxovir 500 mg twice daily.[31]

Two recently completed trials evaluated amdoxovir efficacy. ACTG A5118 was a randomized, double-blind, placebo-controlled trial that compared amdoxovir 300 mg twice daily with enfuvirtide to placebo with enfuvirtide in patients who have failed therapy that included at least 2 NRTIs, 2 PIs, and 1 NNRTI. Interim results at Week 24 showed no significant difference in viral load decline or CD4 increase.[32]

ACTG A5165 was a 96-week, randomized, double-blind trial in 40 heavily pretreated patients with highly NRTI-resistant HIV. Ninety percent of patients were male, all patients were experiencing treatment failure, and the baseline viral load was greater than 2000 copies/ml. This study compared amdoxovir 500 mg twice daily to amdoxovir with MMF when added to failing treatment regimens not including abacavir. Interim results at Day 14 showed a significant overall viral load decline of 0.26 log with no difference between treatment arms. Amdoxovir alone reduced viral load by 0.37 log, and amdoxovir with MMF reduced viral load by 0.23 log. Ten patients experienced viral load reduction of at least 0.5 log (35% of amdoxovir alone arm and 15% of combination arm). Four patients with K65R or Q151M mutations did not respond to treatment with amdoxovir alone. Virologic response was associated with fewer than 5 NRTI mutations or fewer than 4 thymidine analog mutations (TAMs).[33] [34]

Adverse Events/Toxicity

The major toxicity observed with amdoxovir use in animal studies was obstructive nephropathy and was more frequent in small, water-conserving species such as mice, rats, and marmoset monkeys. In cynomolgus monkeys, which like humans produce less concentrated urine, there was no evidence of obstructive nephropathy at doses up to fivefold higher than the anticipated human dose. Obstructive nephropathy was reversible when detected early and dosing was stopped. Hyperglycemia was observed in some monkeys that had signs of renal toxicity, and early cataract formation was detected in several monkeys with hyperglycemia.[35]

Amdoxovir appears generally well tolerated in humans. In clinical trials, the most frequently reported adverse effects were headache, nausea, and diarrhea.[36] Most adverse effects were mild, transient, and unlikely to be drug-related. Few treatment-emergent Grade 3 or 4 adverse events or laboratory toxicities have been reported.[37] [38] [39]

Amdoxovir

Adverse Events/Toxicity (cont.)

Amdoxovir with or without MMF was considered safe and well tolerated based on the results of ACTG A5165. No Grade 2 or greater renal or glucose toxicities were observed, and no lens opacities occurred in that study.[40] [41] In ACTG A5118, a randomized study of amdoxovir 300 mg twice daily given with or without enfuvirtide, Grade 3 and 4 adverse events were similar between arms, and no ocular opacities occurred.[42]

In an early study of amdoxovir, a patient with a history of kidney stones had an episode of renal colic and passed a kidney stone on Day 1. His creatinine levels were normal, and he completed the study with no change in study medication and with no additional renal problems.[43] In another study, one patient experienced shortness of breath with chest tightness and discomfort; all symptoms resolved on Day 16 after completing the 14-day dosing part of the study. In this study, no serum creatinine or glucose levels were elevated greater than Grade 1, and few treatment-emergent Grade 3 or 4 toxicities occurred. One patient in each group experienced Grade 3 or 4 increased triglyceride levels. Additionally, five patients discontinued treatment because they experienced lens opacities that were detected by an ophthalmologist but did not impact visual acuity.[44] [45]

Drug and Food Interactions

In vitro, amdoxovir's active metabolite, DXG, has synergistic antiviral activity with a variety of other antiretroviral compounds.[46]

Mycophenolic acid (MPA), the active metabolite of the immunosuppressant drug MMF, enhances the anti-HIV activity of amdoxovir in vitro. MPA appears to increase inhibition of viral replication by DXG and to reverse resistance observed in isolates with K65R, L74V, and Q151M mutations.[47]

Concurrent administration of amdoxovir, enfuvirtide, and tenofovir disoproxil fumarate [48] amdoxovir and MMF [49] in HIV infected patients have been evaluated in clinical trials.

MPA and ribavirin inhibit synthesis of guanosine nucleotides by inhibiting inosine monophosphate dehydrogenase (IMPDH). Reduction of IMPDH may increase the intracellular concentration of DXG and assist inhibition of HIV replication.[50] Additionally, MPA inhibits deoxyguanosine-triphosphate (dGTP), the natural substrate that DXG-triphosphate competes with the viral enzyme-nucleic acid complex for binding; thus, MPA enhances the ability of DXG to bind to the complex. In one study, both MPA and ribavirin decreased amdoxovir concentrations required for effectiveness by at least tenfold and completely reversed resistance observed with viral mutations.[51] Ribavirin and MPA also increased the anti-HBV activity of several guanine-based nucleoside analogues, including amdoxovir.[52]

Contraindications

Patients with renal insufficiency may be at great risk for obstructive nephropathy and should not be dosed with amdoxovir until additional clinical testing is completed.[53]

Clinical Trials

For information on clinical trials that involve Amdoxovir, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Amdoxovir AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[54]

Dosage Form: Capsules containing amdoxovir 150 mg [55] or 250 mg.[56]

In clinical trials, amdoxovir has been tested at dosages of 100, 200, 300, or 500 mg twice daily or 600 mg once daily as monotherapy, or with 300 or 500 mg twice daily in addition to existing ARV treatment.[57] [58] [59] [60]

Storage: Store between 15 C and 30 C (59 F and 86 F).[61] [62]

Chemistry

CAS Name: 1,3-Dioxolane-2-methanol, 4-(2,6-diamino-9H-purin-9-yl)-, (2R,4R)-[63]

Amdoxovir

Chemistry (cont.)

CAS Number: 145514-04-1[64]

Molecular formula: C9-H12-N6-O3[65]

C 42.86%, H 4.79%, N 33.32%, O 19.03%[66]

Molecular weight: 252.23[67]

Other Names

DAPD[68]

AMDX[69]

Further Reading

Borroto-Esoda K, Myrick F, Feng J, Jeffrey J, Furman P. IN vitro combination of amdoxovir and the inosine monophosphate dehydrogenase inhibitors mycophenolic acid and ribavirin demonstrates potent activity against wild-type and drug-resistant variants of human immunodeficiency virus type 1. Antimicrob Agents Chemother 2004;48(11):4387-94.

Jeffrey JL, Feng JY, Qi CC, Anderson KS, Furman PA. Dioxolane guanosine 5'-triphosphate, an alternative substrate inhibitor of wild-type and mutant HIV-1 reverse transcriptase. Steady state and pre-steady state kinetic analyses. J Biol Chem. 2003 May 23; 278(21): 18971-9. Epub 2003 Mar 21.

Thompson MA, Dessler HA, Eron JJ Jr, Jacobson JM, Adda N, Shen G, Zong J, Harris J, Moxham C, Rousseau FS; DAPD-101 Study Group. Short-term safety and pharmacodynamics of amdoxovir in HIV-infected patients. AIDS. 2005 Oct 14;19(15):1607-15.

Tremblay CL, Poulin DL, Hicks JL, Selliah S, Chamberland A, Giguel F, Kollmann CS, Chou TC, Dong H, Hirsch MS. Favorable interactions between enfuvirtide and 1-beta-D-2,6-diaminopurine dioxolane in vitro. Antimicrob Agents Chemother. 2003 Nov; 47(11): 3644-6.

Manufacturer Information

Amdoxovir
RFS Pharma, LLC
1860 Montreal Road
Tucker, GA 30084
(404) 601-1430

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

References

1. Conf Retroviruses Opportunistic Infect. - 10th, 2003. Abstract 554.

2. RFS Pharma - RFS Pharma Announces 2-Week Data from an NIH-Sponsored Phase 2 Clinical Trial Evaluating Amdoxovir (AMDX) in Highly Treatment-Experienced HIV-1 Infected Individuals [press release], February 14, 2006. Available at: http://www.rfspharma.com/RFSPharma/ACTG5165_press_release_021406.pdf. Accessed 08/31/06.

3. Conf Retroviruses Opportunistic Infect. - 13th, 2006. Abstract 517.

4. AIDS - 2005;19(15):1607-15

5. AIDS - 2005;19(15):1607-15

6. ClinicalTrials.gov - Adding New Drugs for HIV Infected Patients Failing Current Therapy. Available at: http://clinicaltrials.gov/ct/show/NCT00031044. Accessed 08/31/06.

7. Conf Retroviruses Opportunistic Infect. - 12th, 2005. Abstract 553.

8. RFS Pharma - RFS Pharma Announces 2-Week Data from an NIH-Sponsored Phase 2 Clinical Trial Evaluating Amdoxovir (AMDX) in Highly Treatment-Experienced HIV-1 Infected Individuals [press release], February 14, 2006. Available at: http://www.rfspharma.com/RFSPharma/ACTG5165_press_release_021406.pdf. Accessed 08/31/06.

9. Conf Retroviruses Opportunistic Infect. - 13th, 2006. Abstract 517.

10. RFS Pharma - RFS Pharma Announces 2-Week Data from an NIH-Sponsored Phase 2 Clinical Trial Evaluating Amdoxovir (AMDX) in Highly Treatment-Experienced HIV-1 Infected Individuals [press release], February 14, 2006. Available at: http://www.rfspharma.com/RFSPharma/ACTG5165_press_release_021406.pdf. Accessed 08/31/06.

11. Gilead Sciences - Gilead, Emory University and the University of Georgia Research Foundation End Licensing Agreement for Amdoxovir, Investigational Agent for HIV [press release], January 28, 2004. Available at: http://www.gilead.com/wt/sec/pr_1075260536. Accessed 08/31/06.

12. RFS Pharma - About Us. Available at: http://www.rfspharma.com/RFSPharma/About_Us.htm. Accessed 08/31/06.

13. RFS Pharma - Technology: HIV. Available at: http://www.rfspharma.com/RFSPharma/Technology.htm. Accessed 08/31/06.

14. Antimicrob Agents Chemother - 2003 Jun; 47(6):1842-52.

15. Protocol ID: ACTG A5118 - Version 5.0, p. 15

16. RFS Pharma - RFS Pharma Announces 2-Week Data from an NIH-Sponsored Phase 2 Clinical Trial Evaluating Amdoxovir (AMDX) in Highly Treatment-Experienced HIV-1 Infected Individuals [press release], February 14, 2006. Available at: http://www.rfspharma.com/RFSPharma/ACTG5165_press_release_021406.pdf. Accessed 08/31/06.

17. IAS Conf on HIV Pathogenesis and Treatment - 14th, 2006. Abstract We3735.

18. J Acquir Immune Defic Syndr - 2002 Jan 1;29(1):11-20

19. AIDS - 2005;19(15):1607-15

20. Medscape - Experimental NRTI Amdoxovir Well Tolerated, Possibly Effective Against HIV [press release], November 21, 2005. Available at: http://www.medscape.com/viewarticle/517534. Accessed 08/31/06.

21. Medscape - Experimental NRTI Amdoxovir Well Tolerated, Possibly Effective Against HIV [press release], November 21, 2005. Available at: http://www.medscape.com/viewarticle/517534. Accessed 08/31/06.

22. Protocol ID: ACTG A5118 - Version 5.0, pp. 16, 28

23. Protocol ID: ACTG A5165 - Version 4.0, pp. 16-7

24. Antimicrob Agents Chemother - 1999 Oct;43(10):2376-82

25. J Acquir Immune Defic Syndr - 2002 Jan 1;29(1):11-20

26. Antimicrob Agents Chemother - 2000 Jul;44(7):1783-8

27. Antimicrob Agents Chemother - 2000 Jul;44(7):1783-8

28. RFS Pharma - RFS Pharma Announces 2-Week Data from an NIH-Sponsored Phase 2 Clinical Trial Evaluating Amdoxovir (AMDX) in Highly Treatment-Experienced HIV-1 Infected Individuals [press release], February 14, 2006. Available at: http://www.rfspharma.com/RFSPharma/ACTG5165_press_release_021406.pdf. Accessed 08/31/06.

29. Protocol ID: ACTG A5118 - Version 5.0, pp. 16-7

30. Conf Retroviruses Opportunistic Infect. - 10th, 2003. Abstract 554.

31. AIDS - 2005;19(15):1607-15

32. Conf Retroviruses Opportunistic Infect. - 12th, 2005. Abstract 553.

33. RFS Pharma - RFS Pharma Announces 2-Week Data from an NIH-Sponsored Phase 2 Clinical Trial Evaluating Amdoxovir (AMDX) in Highly Treatment-Experienced HIV-1 Infected Individuals [press release], February 14, 2006. Available at: http://www.rfspharma.com/RFSPharma/ACTG5165_press_release_021406.pdf. Accessed 08/31/06.

34. Conf Retroviruses Opportunistic Infect. - 13th, 2006. Abstract 517.

35. Protocol ID: ACTG A5118 - Version 5.0, p. 16

36. Medscape - Experimental NRTI Amdoxovir Well Tolerated, Possibly Effective Against HIV [press release], November 21, 2005. Available at: http://www.medscape.com/viewarticle/517534. Accessed 08/31/06.

37. Conf Retroviruses Opportunistic Infect. - 12th, 2005. Abstract 553.

38. AIDS - 2005;19(15):1607-15

39. Conf Retroviruses Opportunistic Infect. - 13th, 2006. Abstract 517.

40. RFS Pharma - RFS Pharma Announces 2-Week Data from an NIH-Sponsored Phase 2 Clinical Trial Evaluating Amdoxovir (AMDX) in Highly Treatment-Experienced HIV-1 Infected Individuals [press release], February 14, 2006. Available at: http://www.rfspharma.com/RFSPharma/ACTG5165_press_release_021406.pdf. Accessed 08/31/06.

41. Conf Retroviruses Opportunistic Infect. - 13th, 2006. Abstract 517.

42. Conf Retroviruses Opportunistic Infect. - 12th, 2005. Abstract 553.

43. Protocol ID: ACTG A5118 - Version 4.0, p. 18

44. Conf Retroviruses Opportunistic Infect. - 10th, 2003. Abstract 554.

45. Protocol ID: ACTG A5118 - Version 5.0, p. 18

46. Protocol ID: ACTG A5118 - Version 5.0, p. 15

47. IAS Conf on HIV Pathogenesis and Treatment - 14th, 2006. Abstract We3735.

48. Protocol ID: ACTG A5118 - Version 5.0, p. 15

49. Protocol ID: ACTG A5165 - Version 4.0, p. 16

50. IAS Conf on HIV Pathogenesis and Treatment - 14th, 2006. Abstract We3735.

51. Antimicrob Agents Chemother - 2004;48(11):4387-94

52. Antiviral Res - 2000 Nov;48(2):117-24

53. Protocol ID: ACTG A5165 - Version 4.0, p. 17

54. Protocol ID: ACTG A5165 - Version 4.0, p. 17

55. Protocol ID: ACTG A5118 - Version 5.0, p. 37

56. Protocol ID: ACTG A5165 - Version 4.0, p. 41

57. Conf Retroviruses Opportunistic Infect. - 12th, 2005. Abstract 553.

58. Conf Retroviruses Opportunistic Infect. - 13th, 2006. Abstract 517.

59. Medscape - Experimental NRTI Amdoxovir Well Tolerated, Possibly Effective Against HIV [press release], November 21, 2005. Available at: http://www.medscape.com/viewarticle/517534. Accessed 08/31/06.

60. AIDS - 2005;19(15):1607-15

61. Protocol ID: ACTG A5118 - Version 5.0, p. 37

62. Protocol ID: ACTG A5165 - Version 4.0, p. 41

63. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 08/31/06.

64. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 08/31/06.

65. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 08/31/06.

66. Calculation. -

67. Calculation. -

68. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 08/31/06.

69. RFS Pharma - Clinical Research. Available at: http://www.rfspharma.com/RFSPharma/Clinical_Research.htm. Accessed 08/31/06.